

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
23 December 2004 (23.12.2004)

PCT

(10) International Publication Number  
WO 2004/111045 A1

(51) International Patent Classification<sup>7</sup>: C07D 409/14

(21) International Application Number:  
PCT/EP2004/006603

(22) International Filing Date: 17 June 2004 (17.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0314373.2 19 June 2003 (19.06.2003) GB

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BORTHWICK,

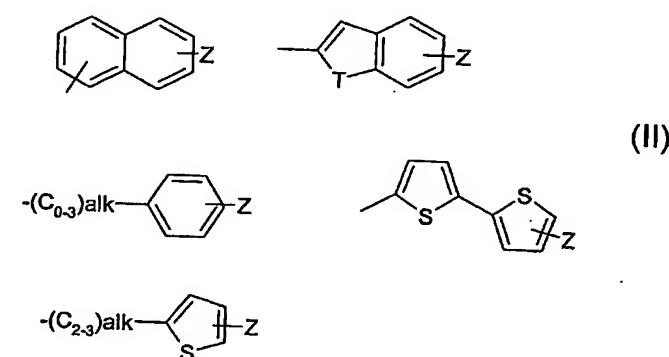
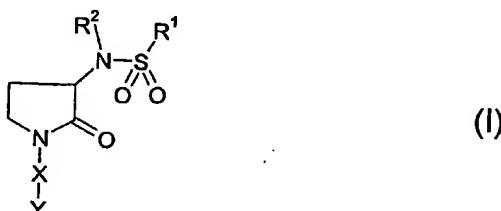
Alan, David [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). KELLY, Henry, Anderson [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). WATSON, Nigel, Stephen [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). YOUNG, Robert, John [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB).

(74) Agent: BAKER, Suzanne, Jane; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,

[Continued on next page]

(54) Title: PYRROLIDINE - 2- ONES AS FACTOR XA INHIBITORS



(57) Abstract: The invention relates to compounds of formula (I): wherein: R<sup>1</sup> represents a group selected from: formula (II), each ring of which optionally contains a further heteroatom N, Z represents an optional substituent halogen, alk represents alkylene or alkenylene, T represents S, O or NH; R<sup>2</sup> represents hydrogen, -C<sub>1-6</sub>alkyl, -C<sub>1-3</sub>alkyl-CO NR<sup>a</sup>R<sup>b</sup>, -C<sub>1-3</sub>alkylCO<sub>2</sub>C<sub>1-4</sub>alkyl, -CO<sub>2</sub>C<sub>1-4</sub>alkyl or -C<sub>1-3</sub>alkylCO<sub>2</sub>H; R<sup>a</sup> and R<sup>b</sup> independently represent hydrogen, -C<sub>1-6</sub>alkyl, or together with the N atom to which they are bonded form a 5-, 6- or 7- membered non-aromatic heterocyclic ring optionally containing an additional heteroatom selected from O, N or S, optionally substituted by -C<sub>1-4</sub>alkyl, and optionally the S heteroatom is substituted by O, i.e. represents S(O)<sub>n</sub>; n represents 0-2; X represents phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: halogen, -C<sub>1-4</sub>alkyl, -C<sub>2-4</sub>alkenyl, -CN, -CF<sub>3</sub>, -NR<sup>a</sup>R<sup>b</sup>, -C<sub>0-4</sub>alkylOR<sup>c</sup>, -C(O)R<sup>f</sup> and -C(O)NR<sup>a</sup>R<sup>b</sup>; R<sup>c</sup> represents hydrogen or -C<sub>1-6</sub>alkyl; R<sup>f</sup> represents -C<sub>1-6</sub>alkyl; Y represents phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is substituted by a group -C<sub>1-2</sub>alkylNR<sup>c</sup>R<sup>d</sup>. R<sup>c</sup> and R<sup>d</sup>, together with the nitrogen atom to which they are bonded, form a 4-membered heterocyclic ring optionally substituted by halogen, OH or -OC<sub>1-6</sub>alkyl, or a 5- or 6- membered non-aromatic heterocyclic ring substituted by OH, -OC<sub>1-6</sub>alkyl or 1 to 2 halogens, with the proviso that the substituent is not attached to a ring carbon atom adjacent to a heteroatom; and/or pharmaceutically acceptable derivatives thereof. The invention also relates to processes for the preparation of compounds of formula (I), pharmaceutical compositions containing compounds of formula (I) and to the use of compounds of formula (I) in medicine, particularly in the amelioration of a clinical condition for which a Factor Xa inhibitor is indicated.

WO 2004/111045 A1



TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**Published:**

— *with international search report*